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Inactivated COVID-19 vaccines: potential concerns of antibody-dependent enhancement and original antigenic sin

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ABSTRACT

Inactivated vaccine is one of the platforms employed in COVID-19 vaccines. Inactivated vaccines have been associated with concerns of antibody-dependent enhancement (ADE) and original antigenic sin (OAS), which are related to non-neutralising or poorly neutralising antibodies against the pathogen. Since inactivated COVID-19 vaccines use whole-SARS-CoV-2 virus as the immunogen, they are expected to generate antibodies against non-spike structural proteins, which are highly conservative across variants of SARS-CoV-2. These antibodies against non-spike structural proteins have found to be largely non-neutralising or poorly neutralising in nature. Hence, inactivated COVID-19 vaccines could possibly be associated with ADE and OAS, especially as novel variants emerge. This article explores the potential concern of ADE and OAS in the context of inactivated COVID-19 vaccine, and outlines the future research directions.

1. Introduction

In response to the COVID-19 pandemic, vaccines of various platforms for protection against SARS-CoV-2 infection have been invented. Inactivated vaccines have a long history of use against various pathogens. With the mature production technique, ease of production, less stringent storage requirement (2–8°C) and the potential of generating more diverse immunity towards various components of the whole virion, the inactivated vaccine platform has been employed in some of the COVID-19 vaccines (for example, CoronaVac by Sinovac and Covaxin by Bharat Biotech) [1]. Its advantage of modest storage requirement is particularly important for countries and regions with limited ultra-cold storage facilities [2]. Yet, from past experience in SARS-CoV, dengue virus, measles and respiratory syncytial virus vaccines, inactivated vaccines are associated with concerns of antibody-dependent enhancement (ADE) [3]. From previous experience in influenza vaccines, original antigenic sin (OAS) is another possible hurdle for booster doses with variant strains [4]. In this article, concerns of ADE and OAS of inactivated COVID-19 vaccines are discussed. Future research directions are also explored.

2. Antibody-dependent enhancement (ADE) in the context of inactivated COVID-19 vaccines

Inactivated vaccines have a long history of use against other pathogens. Yet, from past experience, they are associated with concerns of ADE [3]. ADE is the phenomenon of disease exacerbation in subsequent infections by the pathogen mediated by non-neutralising antibodies against the pathogen produced by immune response in the first or previous encounters with the pathogen [5]. There are two major mechanisms of ADE; the first one is ADE via enhanced infection, which the entry of the pathogen to host cells expressing Fc receptors (such as macrophages) is enhanced as the Fab region of the antibody binds to the antigen on the pathogen while the Fc region binds to Fc receptors on the host cell, hence facilitating pathogen replication and virulence; examples include an old Dengue vaccine [6]. Another mechanism of ADE, known as ADE via enhanced immune activation, is associated with non-neutralising or poorly neutralising antibodies resulting in excessive Fc effector mechanism activation and pro-inflammatory cytokine release leading to enhanced inflammation and damage to host cells; examples include some old respiratory syncytial virus vaccines and measles vaccines [6]. The ADE effects of non-neutralising or poorly neutralising antibodies were related to the use of formalin as the inactivating agent and the generation of a Th2-skewed cytokine profile in recipients, which resulted in low levels of neutralising antibodies

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Abbreviations

ADE	antibody-dependent enhancement
OAS	original antigenic sin

generated [7]. Formalin inactivates viruses mainly by protein-crosslinking; the inactivation process can lead to the formation of free radicals, resulting in extra-conformational changes and carbonylation of viral proteins, which contribute to the unwanted Th2-skewed immune response [8,9]. Beta-propiolactone inactivates viruses mainly by irreversible alkylation of nucleic acid bases, with minimal protein-crosslinking and better preservation of antigen structures under optimal reaction conditions [10]; hence, beta-propiolactone inactivation is expected to carry lower risk of unwanted Th2-skewed immune response and result in better generation of neutralising antibodies [8,11]. Current inactivated COVID-19 vaccines which gained emergency authorisation by WHO used beta-propiolactone as the inactivating agent [12–14]. CoronaVac by Sinovac and Covaxin by Bharat Biotech have been found to generate a Th1-skewed cytokine profile and high neutralising antibody titres in recipients [12,14].

Although ADE after receiving currently authorised inactivated COVID-19 vaccines has not been reported, the possibility of ADE as more novel variants of SARS-CoV-2 emerge should not be neglected. Inactivated COVID-19 vaccines using whole inactivated SARS-CoV-2 as the immunogen are expected to give rise to antibodies against the spike protein (S) antigen as well as other structural protein antigens including the envelope protein (E), matrix protein (M) and nucleocapsid protein (N) antigens [15]. Data of SARS-CoV, which has a similar structure as SARS-CoV-2 showed that only antibodies against the S protein, but not antibodies against the E or M surface structural proteins exhibit neutralising property against the whole virus [16]. Therefore, non-neutralising or poorly neutralising antibodies against SARS-CoV-2 are likely to be formed after vaccination by inactivated COVID-19 vaccines. In case of subsequent encounter with the virus, as long as the concentration of neutralising antibodies is high, the non-neutralising antibodies are overwhelmed and do not exhibit the ADE effects. However, variants of SARS-CoV-2 rapidly emerge as the COVID-19 pandemic persists; and most mutations of the virus occur in the spike protein, while the other structural proteins are relatively more conserved [17]. Therefore, variants arising in the future may become sufficiently antigenically different in the spike protein to escape from binding by the originally 'neutralising antibodies', meanwhile the non-neutralising or poorly neutralising antibodies, especially those targeting the highly conserved E, M or N antigens could still recognise such variants. In this case, ADE would be possible. Vaccination with CoronaVac by Sinovac, one of the inactivated COVID-19 vaccines was found to significantly increase the anti-N antibody titre [18]. The concern of ADE is augmented by the findings that higher anti-N antibody levels are associated with poor outcomes including increased disease severity, oxygen supplementation requirement, duration of hospitalisation, intensive care unit (ICU) admission and increased duration of ICU admission, as well as mortality among COVID-19 infected individuals, which may be due to ADE [19–23]. These serve as warnings for the potential occurrence of ADE in individuals who received inactivated COVID-19 vaccines upon infection by variants of the virus in the future.

Theoretically, mRNA, viral vector and protein subunit COVID-19 vaccines might be less subject to the concern of ADE, as they only code for or contain a component of the virus, mostly the spike protein [24]. Antibodies against other structural proteins are not formed after vaccination. Therefore, these COVID-19 vaccines might be less likely to give rise to non-neutralising or poorly neutralising antibodies against conserved regions of other structural proteins that might mediate ADE upon infection by variants of SARS-CoV-2 in the future.

3. Original antigenic sin (OAS) in the context of inactivated COVID-19 vaccines

OAS is another potential concern in inactivated COVID-19 vaccines, especially in the development of second-generation COVID-19 vaccines against variants of SARS-CoV-2. OAS is a phenomenon first described in influenza virus infection and vaccination, which the immune response against the first strain of the virus encountered is the strongest, despite subsequent infections by or vaccinations against other strains [4]. The consequence is that subsequent infections by or vaccinations against other strains would confer less protective immunological responses and memories against those other strains [25]. The mechanism is illustrated in the following example. After the first encounter (infection or vaccination) with a certain strain 'X' of a virus, antibodies and memory B cells with specificity against various parts of strain 'X' of the virus are produced [26]. Upon subsequent encounter with a variant strain 'Y' of the virus, antibodies against conserved regions that are present in both strains 'X' and 'Y', either remained in the circulation since the first encounter with strain 'X' or quickly produced from plasmablasts differentiated from memory B cells with specificity against strain 'X', will bind to those conservative regions of strain 'Y', making strain 'Y' pathogens less readily available to trigger naïve B-cell response to generate strain 'Y'-specific antibodies and memory B cells [26]. Therefore, the overall immunological response and memory against the virus are less protective against strain 'Y' compared with that generated if strain 'Y' is the first strain encountered [26].

Inactivated COVID-19 vaccines are expected to give rise to antibodies against conserved regions of structural proteins of SARS-CoV-2. As a result, effectiveness of second-generation COVID-19 vaccines using inactivated variants of the virus as the immunogen might be limited by OAS among individuals who received inactivated COVID-19 vaccines in the past, as the antibodies against conserved regions of structural proteins of SARS-CoV-2 can bind to the same conservative regions of structural proteins of the inactivated variant of the second-generation vaccine, which could lead to 'repertoire freeze', that is, limiting the availability of the inactivated variant to trigger naïve B-cell response to generate variant-specific antibodies and memory B cells [26]. There has already been evidence that repeated vaccination with inactivated COVID-19 vaccines could lead to OAS. Upon Omicron BA.2 breakthrough infection, patients who had received a third (booster) dose of inactivated COVID-19 vaccine had significantly higher neutralising antibody titres against the original (wild-type) strain, but significantly lower neutralising antibody titres against Omicron BA.2 compared to patients who had received only two doses of inactivated COVID-19 vaccine; repeated vaccination with inactivated COVID-19 vaccines likely resulted in higher levels of antibodies against the conservative regions of structural proteins of SARS-CoV-2, hence leading to greater 'repertoire freeze' upon subsequent encounter with the Omicron variant [27]. Analogous to a variant breakthrough infection, similar phenomenon of OAS would be expected when individuals receive a booster dose of second-generation COVID-19 vaccine using inactivated variants.

Based on the experience from influenza vaccines, mRNA, viral vector and protein subunit COVID-19 vaccines as second-generation vaccines against variants of SARS-CoV-2 might be subject to less influence by OAS, because they only involve a single component of the virus, that is, mostly the spike protein, which is the most variable region among variants of SARS-CoV-2 [25,26]. Sufficiently antigenically different spike proteins from mRNA, viral vector or protein subunit COVID-19 vaccines (i.e., in the absence of the highly conservative non-spike components) might be able to trigger greater naïve B cell response, thus minimising repertoire freeze and the limitation by OAS.

4. Future directions

Despite the potential concerns of ADE and OAS, currently the overall benefits of inactivated COVID-19 vaccines still greatly outweigh the

risks. Nonetheless, clinical studies to continuously monitor severe cases of COVID-19 for the occurrence of ADE are needed in order to characterise the risk factors associated, including the possible link to COVID-19 vaccination. On top of that, larger scale studies to compare the humoral and cell-mediated immunological response elicited by inactivated COVID-19 vaccines and those of other platforms are needed, in order to deepen our understanding on the strengths and short-comings of different vaccine platforms in the context of COVID-19, hence monitoring for the phenomenon of OAS and optimising the selection of second-generation COVID-19 vaccines against variants of SARS-CoV-2.

5. Conclusion

In conclusion, since inactivated COVID-19 vaccines use inactivated whole SARS-CoV-2 as the immunogen, there is concern of possible ADE upon infection by novel variants in the future. This property of inactivated vaccines may also limit their potential as second-generation COVID-19 vaccines against variants of SARS-CoV-2 due to OAS. More research to characterise the immunological mechanisms of inactivated COVID-19 vaccines and clinical characteristics of vaccinated COVID-19-infected individuals are needed to fill the current knowledge gap.

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Data statement

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Declaration of Competing Interest

The authors have no conflict of interest in relation to this work.

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